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TITLE: Multimodal Intervention Trial for Cognitive Deficits in Neurofibromatosis Type 1:
Efficacy of Computerized Cognitive Training and Stimulant Medication

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14. ABSTRACT During this research period, we successfully coordinated with three participating sites to obtain local IRB approval, submitted personnel and minor administrative amendments, and coordinated with one site for the IRB continuing review. We have maintained a trained study staff which enabled us to recruit 16 participants, conduct 16 baseline assessments, coach 12 participants through the computerized training intervention, and conduct 12 follow-up assessments. In addition, all data has been entered into the research database.					
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1. INTRODUCTION: The purpose of this research is to assess the efficacy of a home-based, computerized cognitive training (CT) program in a sample of 90 children aged 8-16 with NF1 and working memory difficulties. Participants will be stratified by stimulant medication use and randomized equally between two computerized cognitive training interventions within stratum. Participants will be in the study for up to 11 weeks. Each participant will be assigned a computerized training coach who will work with them weekly via a telephone call to provide trouble-shooting, brainstorm strategies for maintaining motivation, and provide feedback on training progress to date. Improving working memory difficulties may help to offset problems with intellectual quotient, executive functioning, and academic performance in children with NF1 over time. Given the high incidence and burdens of attention and WM problems in children with NF1, identifying feasible and efficacious interventions is a critical priority.

2. KEYWORDS: neurofibromatosis, cognition, pediatric, computerized training programs, working memory

3. ACCOMPLISHMENTS:

What were the major goals of the project?

As stated in the approved SOW, the major goals of the project included 1) developing a plan for patient recruitment and human subjects approval; 2) identification and training of study personnel and database initial activities; 3) participant recruitment, therapy, and participant evaluation, and 4) cleaning and analyzing data from patient recruitment, evaluations, safety data, and neuropsychological data, specifically reviewing data monthly for completeness and accuracy and resolving queries with sites.

What was accomplished under these goals?

Our first major task was to continue coordinating with other sites regarding patient recruitment and human subject approval. While the statement of work indicates these activities should have been completed in the first year, we experienced delays and activities have continued into year two. This year, we successfully coordinated with other sites regarding material transfer agreements and clinical trial agreements submission; coordinated with three participating sites related to submitting the study for local IRB approval; maintained compliance by submitting personnel and minor administrative amendments; and coordinated with one site for annual IRB report for continuing review.

- CNHS: Continuing Review approved May 1, 2017
- CHLA: HRPO protocol approved on May 15, 2017; Continuing review approved October 10, 2017

- The Royal Children's Hospital Melbourne: Local IRB approved on May 23, 2017; HRPO protocol application submitted September 19, 2017
- The Children's Hospital at Westmead: Local IRB approved on May 23, 2017; HRPO protocol application submitted September 19, 2017
- Boston: Undergoing IRB protocol development

As for stated goals not met, we did not coordinate with one site for IRB protocol submission. The PI at Boston has experienced adverse personal events which have delayed the development of an IRB protocol submission. On June 12, 2017, we conducted an investigators meeting in conjunction with the Children's Tumor Foundation annual meeting, held in Washington, DC. All co-investigators from all participating sites were in attendance, including the PI from our Boston site. At the meeting, we discussed IRB protocol delays and received confirmation that Boston is ready to move forward with local IRB protocol development and submission. Research coordinators at CNHS are currently working with the PI at Boston to develop the local IRB protocol. In addition, we submitted HRPO approval applications for the Melbourne and Westmead sites on September 19, 2017, but we have not yet obtained DOD HRPO approval.

Our second major task was the continued training of study personnel and maintenance of the clinical database. With regards to the identification and training of study personnel, we have completed the training of all study personnel. In year two, we experienced staff turnover but maintained available assessment and intervention clinicians and coordinators by training new staff. We have successfully coordinated with four sites for Cogmed and MobyMax coach training. Two trained Cogmed and MobyMax coaches at our site will provide coaching to all study participants at CNHS and CHLA. One Cogmed and MobyMax coach has been trained in Australia and will provide coaching to participants at the Westmead sites. The coordinating center has also identified an intervention coach at the Melbourne site and training will begin in November 2017. The coordinating site is prepared to provide supervision to the Westmead and Melbourne coaches upon HRPO approval. We as the coordinating site are available to provide supervision of Cogmed and MobyMax coaching to problem-solve coaching issues and refine coaching procedures consistently across sites. Supervision will continue to be provided through interactive conference calls and email.

Our third major task was participant recruitment, therapy, and participant evaluation. In year two, we at CNHS successfully recruited 14 participants, conducted 14 baseline assessments, and 12 participants successfully complete the computerized training intervention and returned for follow-up assessment. None of the participants enrolled to date have been lost to follow up. CHLA also successfully enrolled two participants who underwent baseline testing and qualified to participate in the computerized training intervention. To date, we have recruited a total of 24 participants across two sites and there have been no adverse events associated with study participation. While our goal

for the end of the year was to recruit a total of 63 patients across four sites, we do not believe that the discrepancy between the proposed and actual enrollment to date will affect our ability to fully accrue our targeted number of participants. Specifically, we believe we will quickly progress towards our target accrual once the Sydney and Melbourne sites receive HRPO approval and begin enrolling participants. Additionally, CNHS has achieved 122% of our predicted enrollment and, we already have three additional enrollment visits scheduled in the next quarter. CHLA has also maintained their target enrollment since receiving approval and they have four appointments scheduled within the next quarter. In summary, our main barriers to our original schedule of accrual have been related to obtaining local and HRPO approval. These barriers have largely been resolved, and we anticipate being able to maintain a rate of accrual consistent with, or higher than, originally planned.

The rest of the goals subsumed under the third major task are ongoing, including monitoring recruitment process, retention, and completion of the final assessment; monitoring regulatory compliance (IRB continuing approvals) and GCP compliance; complete follow-up assessments after Cogmed training is complete; and having monthly meetings with all sites to discuss progress and engage in troubleshooting.

Our fourth major task involved cleaning and analyzing data from patient recruitment, evaluations, safety data, and neuropsychological data. Data from participants at CNHS and CHLA are entered into a database by the appropriate team member, where data are reviewed for completeness and accuracy by the database manager. Data inquiries are conducted monthly and reviewed by the primary research coordinator at CNHS. Discrepancies are then identified and rectified. Enrollment is approaching 30 participants and CNHS is preparing to summarize data for review.

The rest of the goals subsumed under the fourth major task are either ongoing or to be performed at a later time. Those that are to be performed at a later time include summarizing data after 60 participants; summarizing all data; performing all analyses per analysis plan; sharing findings with investigators; and disseminating findings through abstracts, presentations, publications and to the funder.

What opportunities for training and professional development has the project provided?

Research coordinators at the coordinating site were given access to the Cogmed professional training program. By completing the program, research coordinators can now serve as intervention coaches for participants who receive the Cogmed intervention. Research coordinators were also given instructor access to MobyMax, which allows coaches to monitor participation in the reading intervention. While an official MobyMax coaching course is unavailable, the PI of this study provides training

and supervision to research coordinators so they can give effective feedback to participants who are receiving the reading comprehension intervention.

How were the results disseminated to communities of interest?

Nothing to report.

What do you plan to do during the next reporting period to accomplish the goals?

During the next quarter, we hope the HRPO is approved for our two Australia sites so they can begin recruiting and enrolling subjects. The sites that are already open will continue recruiting and enrolling subjects. Our goal is to enroll a total of 88 participants by the time of the next annual report, which will be accomplished by enrolling a total of four to five participants each quarter at all four sites. Over the next year, the coordinating site also plans to summarize and review the data after 30 and 60 participants are recruited.

4. IMPACT

What was the impact on the development of the principle disciplines of the project?

CNHS has successfully recruited participants over the past year but CHLA just began recruitment and the other sites are not yet recruiting. As a result, it is too soon to have a sense of the impact of this study on the development of the principle disciplines of the project.

What was the impact on other disciplines?

Nothing to report.

What was the impact on technology transfer?

Nothing to report.

What was the impact on society beyond science and technology?

Nothing to report.

5. CHANGES/PROBLEMS

Changes in approach and reasons for change

In Year two, we did not make any changes in the approach that was approved by the funding agency. Please refer to the annual report for Year one for a summary of the previous protocol changes.

Actual or anticipated problems or delays and actions or plans to resolve them

1) Within the first year, we experienced a myriad of challenges which delayed the timeline of this project. In 2015, Cogmed phased out support for the non-adaptive training, which was previously the active control in this study. As a result, the team researched and identified MobyMax as the new, active control. Due to the unforeseeable circumstances with the active control condition originally planned for the study, the submission of the Coordinating Center protocol to the IRB was significantly delayed. In addition, it took longer than originally anticipated for other sites to obtain IRB approval. IRB analysts and reviewers ultimately requested lengthy documentation of explanations regarding protection of privacy and confidentiality. While we at the coordinating site have exceeded our recruitment goal, the significant delays in IRB approval, contract executions, and HRPO approval within the first year has resulted in recruitment delays in year two. The coordinating center has taken a number of steps over the last year to remedy these delays.

The Principal Investigator at Boston experienced adverse personal events over the past year which has prevented the development of an IRB protocol. We have continued coordination efforts with the site and we are currently developing the IRB protocol. We are confident this will not negatively influence enrollment as this study was originally designed with four sites. With the addition of the second Australian site over the past year, we are able to maintain our original target of four recruitment sites.

It has taken longer than we originally anticipated for Children's Hospital of Los Angeles (CHLA) to obtain HRPO approval, which ultimately delayed recruitment. Their HRPO application was submitted on December 13, 2016 and they received approval five months later on, May 15, 2017. Recruitment began in the fourth quarter and is moving forward at a rapid pace. We anticipate CHLA will continue to recruit at an accelerated rate.

The addition of the second Australian site created unanticipated delays which delayed recruitment at both sites. Sydney and Melbourne received conditional IRB approval in the first quarter of year two, but there were delays in the execution of their subcontracts with our Grants and Contracts office. In addition, we were required to submit a revision of the grant budget to the DOD to account for the addition of the second Australian site. The revision was submitted in December 2016 and the Australian subcontracts were executed on May 23, 2017 for Melbourne and June 2, 2017 for Sydney. The next step was to obtain HRPO approval, which was submitted to the DOD on September 19, 2017. The applications are undergoing DOD review. We contacted the reviewer who indicated the initial review has concluded and the application is currently under review by the HRPO Approval Authority. We were told we should receive feedback by

November 2017. At that time, we hope to receive approval and begin recruitment at our Sydney and Melbourne sites.

While we expected to enroll 63 participants by the end of year two, we have enrolled 24, 38% of our anticipated goal. At CNHS, we have enrolled 22 participants, which exceeds our goal of 18 participants by the end of year two by 122%. We expect to continue enrolling participants at a brisk pace. In addition, CHLA has expedited recruitment efforts and the site has four participants scheduled in the next quarter, which will bring them to a total of six participants enrolled out of an expected 18. Finally, we have increased the recruitment goal at each site to 4-5 participants per quarter, which will enable our study to meet our enrollment goal of 130 participants by the end of year four.

2) At CNHS, the grant is designed to provide per case reimbursements for each participant who undergoes baseline and follow-up testing. In order to maintain institutional compliance, we at the coordinating center are now required to register participants with the Clinical Trials Office (CTO) prior to the scheduled research appointment. The CTO was unfamiliar with how to navigate the per case reimbursement payments with their existing registration system, which has created delays in charging the grant for services which have taken place. The CTO has created another project identification number (PID) which will now be used to pay out the per case reimbursements to providers completing the protocol assessments. We have been in constant communication with the CTO team and the new billing process will soon be initiated for the 22 participants who have been enrolled thus far.

Changes that had a significant impact on expenditures

Nothing to report.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

There were no significant deviations, unexpected outcomes, or changes in approved protocols for the use or care of human subjects, vertebrate animals, biohazards, and/or select agents during the reporting period.

Significant changes in use or care of human subjects

There were no significant deviations, unexpected outcomes, or changes in approved protocols for the use or care of human subjects.

Significant changes in use or care of vertebrate animals

Vertebrate animals are not used in this study.

Significant changes in use of biohazards and/or select agents

There were no significant deviations, unexpected outcomes, or changes in approved protocols for the use or care of biohazards and/or select agents.

6. Products

Nothing to report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

Name:	Maria T. Acosta, M.D.
Project Role:	PI
Researcher Identifier:	ORCID ID 0000-0002-7645-0011
Nearest person month worked:	0.3 per quarter/1.2 per year, cost sharing support by CNMC for an additional 0.3 per quarter /1.2 per year
Contribution to project:	Overseen all details regarding all necessary documents to submit to DoD and IRB
Funding support:	
Name:	Kristina K. Hardy, Ph.D.
Project Role:	Co-PI, Site Investigator
Researcher Identifier:	ORCID ID 0000-0002-5479-5043
Nearest person month worked:	0.6 per quarter/2.3 per year, cost sharing support by CNMC as above
Contribution to project:	Overseeing neuropsychological assessments and intervention methods as outlined in protocol
Funding support:	
Name:	Marni Jacobs, Ph.D.
Project Role:	Lead Statistician
Researcher Identifier:	ORCID ID 0000-0001-6649-6692
Nearest person month worked:	0.23 per quarter/0.9 per year
Contribution to project:	Provided statistical expertise on protocol
Funding support:	
Name:	Dan Zhang (replaced Wenze Tang)
Project Role:	Data Coordinator
Researcher Identifier:	N/A
Nearest person month worked:	0.09 per quarter/.36 per year
Contribution to project:	CRF and EDC creation
Funding support:	

Name:	Kaitlyn Tiplady, M.Ed. (Replaced Katie Olson)
Project Role:	Clinical Research Coordinator
Researcher Identifier:	N/A
Nearest person month worked	1.5 this quarter/6 per year
Contribution to project:	Facilitates communication between all sites, administrative management, coordination of study material and operations, intervention coach
Name:	Anthony Gioia, B.S.
Project Role:	Clinical Research Coordinator
Researcher Identifier:	N/A
Nearest person month worked	0.75 this quarter/3 per year
Contribution to project:	Facilitated communication sites, administrative management, intervention coach

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Nothing to report.

What other organizations were involved as partners?

Nothing to report.

8. SPECIAL REPORTING REQUIREMENTS

None.

9. APPENDICES

None included.